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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BRANNOCK, MICHAEL T	
ART UNIT	**PAPER NUMBER**
1646	22

DATE MAILED: 08/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application N .	Applicant(s)	
	09/724,964	CROMPTON, TESSA	
	Examiner	Art Unit	
	Michael Brannock	1646	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-4 and 6-32* is/are pending in the application.

4a) Of the above claim(s) *3,19,20,22-28 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 2, 4, 6-18, 21, 29, 31, 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application: Claims and Amendments

Applicant is notified that the amendments put forth in Paper 20, 4/8/03, have been entered in full.

Claims 1-4, 6-32 are pending. Claims 3, 19, 20, 22-28 and 30 have been withdrawn previously. Applicant is reminded that the instant claims are being examined only to the extent that they read on the elected invention, i.e., the administration of a benzene modified sonic hedgehog polypeptide for the inhibition of an immune response, as set forth previously.

Withdrawn Rejections:

The rejection of claims 1, 2, 4-18, 21 and 29 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as set forth previously is withdrawn in view of Applicant's amendments.

Maintained Rejections:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 6-18, 21, 29 and new claims 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of suppressing or promoting thymic T-cell maturation comprising administering a polypeptide at least 100%

identical to the N-terminal auto-proteolytic fragment of a hedgehog polypeptide, wherein said peptide binds a naturally occurring patched protein, does not reasonably provide enablement for the broad scope of suppressing or enhancing the immune function or immune system of an animal, nor for modulating T-cell maturation other than in the thymus (e.g. peripheral T-cell maturation), nor for any form of therapy, and nor for the suppression or promotion of T-cell maturation comprising the administration of a hedgehog agonist thereof other than a polypeptide at least 100% identical to the N-terminal auto-proteolytic fragment of a hedgehog polypeptide or antagonistic antibody that binds there to. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to the invention commensurate in scope with these claims.

It is noted that the previous Office action (Paper 19, 1/24/03) indicated that the claims were enabled for administering a polypeptide at least 80% identical to the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide, however this determination was erroneous.

The claims encompass the administration of an essentially limitless number of variants of naturally occurring hedgehog proteins, i.e. proteins with substitutions, deletions or insertions relative to a naturally occurring hedgehog protein. However, the specification has not provided sufficient guidance as to how to make and use the claimed variant polypeptides which are not 100% identical to a naturally occurring hedgehog protein, yet which still retain a desired property of the polypeptide of naturally occurring hedgehog protein . The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Nor has the specification provided guidance as to which of these variants would be useful

for producing antibodies to be used in the claimed methods. If a variant of the naturally occurring hedgehog protein is to have a structure and function similar to the naturally occurring hedgehog protein, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the naturally occurring hedgehog protein.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad.

Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of hedgehog proteins that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

The specification presents results obtained wherein sonic hedgehog was shown to suppress the transition of dissociated fetal thymic T-cells from the CD4-CD8- double negative stage to the double positive stage. Conversely, an anti-hedgehog antibody appeared to promote the transition from the double negative to the double positive stage (e.g. Figures 1-4). The specification, however, only speculates that hedgehog proteins could have similar effects on other aspects of the immune system; and that such effects could be utilized as part of a therapy (e.g. pages 4-5 and 9-12). Further, the specification appears to simply speculate that any or some of the myriad of chemically and functionally disparate compounds that are asserted as being "hedgehog or ptc therapeutics" or agonists thereof could be used to accomplish the recited goals of the claims, yet does not provide sufficient guidance to the skilled artisan to chose among them. Each of the above issues, as well as Applicant's arguments, will be discussed in detail below.

Claims 1, 2, 4-18, 21 and 32 encompass methods of modulating any and all aspects of the immune system, yet the specification has provided sufficient guidance only as the claims relate to methods of modulating T-cell maturation in the thymus. The skilled artisan appreciates that

the immune system comprises an extraordinarily complex and varied array of subsystems and sub-processes which make up those subsystems, as is well established in the art. The instant specification describes some effects of hedgehog signaling on the process of T-cell maturation in the thymus. Yet the claims encompass any and all processes involving the immune system, e.g. B-cell maturation and activation, peripheral T-cell maturation, T-cell activation, etc. (see page 1, for example). The specification provides no teaching as to what can be expected of hedgehog signaling in any process other than thymic T-cell maturation. The specification teaches that hedgehog proteins are antagonists of immune function, e.g. antagonists of T-cell maturation (pg 5, lines 10-16); however, hedgehog proteins are known in the art to act as both positive and negative regulators in an extraordinary variety of developmental and cell-maintenance capacities involving many disparate cell types. Thus, the skilled artisan could not expect to be able predict the effects of hedgehog on any other immune system component simply based on Applicant's disclosed observations regarding the effect of sonic hedgehog on the CD4-CD8- double negative/double positive transition in the thymus. This fact is evidenced, for instance, by Lowery et al., J. Immunology 169(4)1869-75, 1999, who report that sonic hedgehog promotes, rather than inhibits, cell cycle progression in activated peripheral CD4+ T-cells (see the Abstract); an effect opposite to that of the instantly reported effect on T-cell maturation in the thymus. The skilled artisan appreciates that the instant specification provides only an invitation to try and find other effects that hedgehog proteins might have on any other aspect of the immune system. Thus, in order to practice the invention commensurate in scope to that which is claimed, the skilled artisan is provided with nothing more that an invitation to begin an extensive research plan wherein various components of the immune system are tested against the presence

or absence of hedgehog proteins to try to find some effect, and then to try find a way to use that effect for some purpose. Such a call for random trial and error experimentation is unduly burdensome.

At page 8 of Paper 20, Applicant argues that the specification is enabled for in vivo enhancement or suppression of thymic T-cell maturation, however this point has not been disputed. Applicant additionally argues that, absent evidence to the contrary, the sonic hedgehog administration would be expected to suppress the immune system as a whole, as is simply required by the claim. This argument has been fully considered but not deemed persuasive. As discussed above, the relationship between hedgehog and the immune system as a whole is so extraordinarily complex that it is utterly impossible to predict what the net effect would be. The evidence contrary to Applicant's expectations is provided, for example, by Lowery et al. above. Applicant's arguments regarding Lowery et al. have been fully considered but not persuasive. The skilled artisan appreciates that the facts pointed-out by Applicant provide support for the concept that it is simply too difficult to predict the effects of hedgehog administration on the immune system as a whole or in any particular part based on what is known in the art and taught in the specification. The invitation to the skilled artisan to begin to answer these questions experimentally is not adequate guidance to use the invention in a way that meets the requirements of 35 USC 112, first paragraph.

Claim 1 has been amended such that the claim no longer recites a "therapeutic amount" yet claims 1 and 2 require the administration of an amount of hedgehog agonist or antagonist effective to suppress or enhance immune function. As set forth previously the specification does not provide an enabling basis for the scope of these claims, which encompass therapies for

immune disorders as contemplated in the specification. The specification has merely provided a speculation that because sonic hedgehog inhibits the CD4-CD8- double negative/double positive transition *in vitro*, then sonic hedgehog could be used in some form of immune therapy. The skilled artisan appreciates that simply because a substance in inhibits the CD4-CD8- double negative/double positive transition, it does not follow that the substance would be useful in an immune therapy. Ethanol is known in the art to inhibit the CD4-CD8- double negative/double positive transition *in vivo*, yet ethanol is not used in immune therapy (see Dubec et al., ALCOHOL 13(6)55-537, 1996. Thus, the instant specification provides merely an invitation to the highly skilled artisan to begin a research plan to try to determine what effects of hedgehog proteins have on the many different aspects of immune function and on the immune system as a whole.

Applicant argues, essentially, that ethanol does not provide an instructive example in this case because, for example, ethanol does not have a specific receptor and exerts non specific and pleiotropic effects. This argument has been fully considered but not deemed persuasive. It is well established that ethanol does interact with specific receptors and in specific regions of the body, e.g. it potentates specific GABAA receptors in specific brain regions. Regarding pleiotropic effects, i.e. the control, by a single gene, of several distinct and seemingly unrelated phenotypic effects, it is hard to imagine a more pleiotropic molecule than sonic hedgehog. As pointed-out above, sonic hedgehog appears to have pleiotropic effects in not only the immune system but in practically every system that has been studied, e.g. the nervous, muscular and digestive system, as is well established in the art. The point of this is that the skilled artisan might reasonably extrapolate Applicant's in vitro data regarding thymic T-cell maturation and

determine that it is more likely than not that sonic hedgehog administration would suppress thymic T-cell maturation in vivo; but what the effects might be of hedgehog administration on the immune system as a whole or on any particular part, based on what is known in the art and taught in the specification, is utter speculation. As set forth above, The invitation to the skilled artisan to begin to answer these questions experimentally is not adequate guidance to use the invention in a way that meets the requirements of 35 USC 112, first paragraph.

Additionally, Applicant argues that issues of safety and efficacy are not within the purview of the Patent Office. This argument has been fully considered but not deemed persuasive. Nowhere in the rejection has there been any requirement for safety. Nor is there a requirement regarding the *degree* of efficacy. However, to the extent that "efficacy" is synonymous with the ability to *use* the invention, the invention must be capable of working as claimed without undue experimentation according to the requirements of 35 USC 112, first paragraph. The invitation to begin a research plan to try to get the invention to work as claimed does not, in this case, meet the requirements of 35 USC 112, first paragraph.

Additionally, the specification has provide results with the administration of the N-terminal auto-proteolytic fragment of a sonic hedgehog polypeptide or an anti-hedgehog antibody, such fragment being known to bind patched protein, yet the claims comprise an essentially unlimited genus of proteins that would not be expected to bind mammalian patched, e.g. artificial proteins, and proteins being 80% identical the N-terminal fragment or to the full length protein. The claims are not limited to the use of the proteins that could be reasonably expected to bind a naturally occurring patched protein. Further, the claims encompass the administration of any compound that is encompassed by the definition of a hedgehog agonist or

antagonist, i.e., any compound that "binds to patched and alters its signal transduction activity, or compounds which alter the binding and/or activity of a protein (e.g., intracellular) involved in patched signal pathway, and compounds which alter the level of expression of a hedgehog protein, a patched protein or a protein involved in the intracellular signal transduction pathway of patched"(see pages 6 and 41). It is well appreciated that the activities of patched are extremely complex and as yet controversial and incompletely identified (see Stull and Iacovitti, Experimental Neurobiology 169(1)36-43, 2001, especially page 40). The claims claim methods of modulating or suppressing the immune system with hedgehog or ptc therapeutics, yet the specification does not provide sufficient guidance as to which hedgehog or ptc therapeutics are useful modulating any particular aspect of the immune response. The specification puts forth that PKA inhibitors are ptc-therapeutics and that high PKA activity has been shown to antagonize hedgehog signaling (page 48); yet the specification merely invites the artisan to test these PKA inhibitors to try to find ways in which they might effect the immune system. The involvement of PKA, and cAMP in general, in T-lymphocyte maturation and/or activation has been studied *in vitro* for years; such study has revealed a complex and unpredictable relationship between PKA and the activity of T-cells, reviewed in Bryce et al., Immunopharmacology 41(139-146)1999. In fact, Bryce et al. teach that the immunomodulatory effects of cAMP on T-cells do not involve PKA (see the Title) and suggest that the previously reported effects of PKA inhibitors on T-cells (e.g. that of claim 23) are due to nonspecific interactions with other kinases (see col 1 of page 140). The instant specification, has not provided the skilled artisan with more than an invitation to try to find compounds that are encompassed by the term "hedgehog or ptc-therapeutic" and then to try to find effects of the compounds on any aspect of the immune

system. Such essentially random trial and error experimentation is not considered routine by the skilled artisan and would be considered unduly burdensome.

Therefore, due to the lack of direction/guidance presented in the specification regarding which structural features are required of agonist or antagonist in order to provide activity, the absence of working examples directed to same, the complex nature of the effect of compounds disclosed as being hedgehog or ptc therapeutics and the contradictory state of the art (see Stull and Iacovitti, Dubec et al., Lowery et al., and Bryce et al., above), the breadth of the claims which encompass a multitude of distinct and disparate aspects of the immune system, and which encompass a multitude of functionally disparate hedgehog agonists and antagonists, undue experimentation would be required of the skilled artisan to make the claimed invention.

Applicant argues that the specification describes the hedgehog signaling pathway and that this pathway is well known at the time of filing. This argument has been fully considered but not deemed persuasive. First, the examiner is aware of no prior art that asserts that there is only one hedgehog pathway. To the contrary, it is well established that such pathways are extremely complex and varied, as they must have to be to account for the extraordinarily diverse array of the phenotypic effects of the different hedgehog proteins. Second, it does not matter that a pathway has been presented in the specification, as discussed at length above, the pathways involved in the different parts of the immune system, and in the immune system as a whole, are extremely complex and unpredictable. Thus, the mere suggestion that these pathways can be manipulated to achieve a desired end, is simply an invitation to begin this work.

Applicant argues that hedgehog agonists have been described e.g. PKA inhibitors, and could easily be obtained e.g. through high throughput assays, because the proposed functional

characteristics are explicitly detailed in the specification. This argument has been fully considered but not deemed persuasive. First, the skilled artisan appreciates that simply verbalizing or writing down the functional characteristics that a molecule should have, in no way provides one with that molecule. Second, Applicant's confidence in high throughput assays does not appear to be shared by those who practice the art, see Lahana R., Drug Discovery Today, 4(10)447-448, 1999 who answers the question "How many leads have we got from combinatorial chemistry and high-throughput screening so far?" – "none!", see the Title page; see also, Horrobin, DF, British Med. Journal, 322(7280)239, July 2003.

Applicant argues that Stull and Iacovitti, cited by the examiner, is not applicable to the present invention for several reasons. Applicant asserts that none of the experiments of Stull and Iacovitti examine the effects of Shh administration in the absence of FGFs. This argument has been fully considered but not deemed persuasive. Applicant's attention is drawn to page 39, first paragraph of RESULTS, wherein Stull and Iacovitti discuss the results of experiments wherein Shh alone or in combination with FGF is added to the explants. Additionally, Applicant asserts that Stull and Iacovitti do not examine agonizing or antagonizing hedgehog signaling. Although the examiner admits that he may not understand this argument, it is pointed out that the skilled artisan appreciates that examining the effects of hedgehog administration would be considered to be an examination of agonizing hedgehog signaling. Additionally, Applicant argues that applicant's need not explain or describe *why* the invention works; it is sufficient to show that it does. This argument has been fully considered but not deemed persuasive. While Applicant's assertion is technically correct, the fact pattern in the instant case is exactly the reverse of the assertion. The specification theorizes that the invention should work based on several principles,

e.g. that hedgehog signaling can be manipulated by inhibitors of PKA and thus compounds that modulate hedgehog signaling through PKA should be useful for modulating immune functions. Thus, it appears that the specification has described *why* the invention should work but has not shown that it does. Applicant has not shown that the invention works commensurate in scope to that which is claimed. The instant rejection has enumerated many reasons why the skilled artisan would appreciate that the complexity of these systems makes it impossible to readily use the invention without substantial investigative effort, if in fact the invention could ever be made and used commensurate in scope with that which is claimed.

Applicant argues that Bryce et al., cited by the examiner, is not applicable to the instant invention because Bryce et al. do not examine the effect of PKA activity on hedgehog signaling and that they use PKA inhibitors in the presence of elevated cAMP. This argument has been fully considered but not deemed persuasive. The examiner admits that he does not understand the significance of these arguments. The instant specification intends to modulate immune function with PKA inhibitors, Bryce et al. provides evidence that the effect of PKA activity on T-cell maturation is unpredictable, complex, and controversial.

In summary Applicant concludes that the efficacy of the intended methods could be readily evaluated by the skilled artisan. This argument has been fully considered but not deemed persuasive. The specification has merely provided an invitation to begin a research plan to try to find ways to make and use the claimed methods in ways that are encompassed by the claims. Applicant further urges that extensive evidence has been provided in support of the prophetic examples encompassed by the claims. This argument has been fully considered but not deemed persuasive. One skilled in the art would not characterize the two experiments described on page

58-59 as being extensive. They are merely suggestive of future uses, "Tossing out the mere germ of an idea does not constitute enabling disclosure... [R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Genentech, Inc. v. Novo Nordisk Inc., 108 F.3d 1361, 1366, 42 U.S.P.Q.2d 1001, 1005 (Fed. Cir. 1997). Such reasonable detail has not been provided, as discussed above.

Claims 1, 2, 4, 6-18, 21, 29 and new claims 31 and 32 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims require *in vivo* methods of modulating an immune response comprising administering an effective amount of a hedgehog agonist or antagonist, thus encompassing immune therapy. However, there appears to be no description of such a effective amount nor of a genus of hedgehog agonists or antagonists in the specification. The specification appears to base the assertion of potential therapy on the observed effects of sonic hedgehog on T-cell maturation in an *in vitro* thymic cell preparation, e.g. that sonic hedgehog inhibits the CD4-CD8- double negative/double positive transition *in vitro*. The skilled artisan recognizes, however, that simply because a substance inhibits the CD4-CD8- double negative/double positive transition, it does not follow that the substance would be useful in an immune therapy. Ethanol is known in the art to inhibit the CD4-CD8- double negative/double positive transition *in vivo*, yet ethanol is not used in immune therapy (see Dubec et al., ALCOHOL 13(6)55-537, 1996. Thus, based on Applicant's limited disclosure, the skilled artisan would not recognize that Applicant was in

possession of a therapeutic amount of hedgehog for the modulation of the immune system, as is encompassed by the claims.

Nor has the specification sufficiently described a genus of hedgehog agonists and antagonists, that could be expected to function as required by the claimed methods, such that the skilled artisan would recognize that Applicant was in possession of such a large and structurally diverse genes at the time the application was filed.

Applicant argues that hedgehog agonists have been described e.g. PKA inhibitors, and could easily be obtained e.g. through high throughput assays, because the proposed functional characteristics are explicitly detailed in the specification. This argument has been fully considered but not deemed persuasive. First, the skilled artisan appreciates that simply verbalizing or writing down the functional characteristics that a molecule should have, in no way provides one with that molecule. Second, Applicant's confidence in high throughput assays does not appear to be shared by those who practice the art, see Lahana R., Drug Discovery Today, 4(10)447-448, 1999 who answers the question "How many leads have we got from combinatorial chemistry and high-throughput screening so far?" – "none!", see the Title page; see also, Horrobin, DF, British Med. Journal, 322(7280)239, July 2003.

The instant disclosure of a single agonist, i.e. sonic hedgehog protein itself, and a single antagonist, i.e. an antibody against sonic hedgehog, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative

number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, two molecules that have been shown to work in vitro, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

With the exception of the hedgehog polypeptides, including those referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed variants and the undisclosed modulators of hedgehog signaling, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, hedgehog proteins and antibodies there to, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Conclusion

No claims are allowable.

Please note the new official fax number below:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Brannock, Ph.D., whose telephone number is (703) 306-5876. The examiner can normally be reached on Mondays through Thursdays from 8:00 a.m. to 5:30 p.m.The examiner can also normally be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler, Ph.D., can be reached at (703) 308-6564.

Official papers filed by fax should be directed to (703) 872-9306. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

MB

August 8, 2003

YVONNE EYLER, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600